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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,027	05/29/2001	Jinhai Wang	3586.04-1	6751

7590 02/23/2005

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,027	WANG, JINHAI	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,38 and 40-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37, 38, 40-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 1/24/05, claims 37, 38, 40, 47, 54, 55, 59-69 have been amended and claims 39, 70 cancelled. Claims 37, 38, 40-69 are now pending.

Applicants' arguments filed 1/24/05 have been considered and found not persuasive.

✧

The abstract is objected to. The abstract should be no more than about 2/3 of a page. (It is not necessary to fully define the substituent variables). In addition, it is not accurate to state (last sentence of the abstract) that the claimed compounds are "reagents" or "compositions". In addition, the phrase "and the like" should be avoided in an abstract.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-53 and 59-69 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention.

Claim 59 is drawn to the following:

"a caspase inhibitor ...comprising a compound ...[of] the structure:"

This constitutes new matter. This claim can be interpreted to mean that the compound (which exhibits the property of inhibiting caspases) does not merely "consist" of the indicated formula, but rather comprises it. This would mean, for example, that any hydrogen atom in the structure could be deleted and replaced with any group, substituent or moiety. There is, however, no descriptive support for such a proposition in the application as filed.

The same issue as indicated above applies in the case of claim 47 (see line 2 of the claim).

✧

Claims 38, 40-53, 64-69 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown that representative examples of the claimed compounds can inhibit caspases *in vitro*. It is likely to be true that for certain cell types, apoptosis will be inhibited. But the specification gives no guidance as to which cell types will exhibit

reduced apoptosis, and which will not. As it happens, the skilled artisan who has observed inhibition of apoptosis in one cell line (as a consequence of incubation with compound "X") cannot "predict" what other cell lines will undergo reduced apoptosis in the presence of compound "X". The skilled artisan also cannot predict what other cell types will undergo enhanced apoptosis in the presence of compound "X". For example, Fang X. (*Biochemical Journal* **352 Pt 1** 135-43, 2000) discloses that lysophosphatidic acid inhibits apoptosis in fibroblasts; at the same time, Steiner M. R. (*Annals of the New York Academy of Sciences* **905** 132-41, 2000) discloses that lysophosphatidic acid induces apoptosis in neuronal cells. Thus, if a determination is made that a given compound will inhibit apoptosis of a given cell type, the skilled artisan cannot predict the cell types in which apoptosis will be inhibited, and the cell types in which apoptosis will be induced. This conclusion is reinforced by the findings of Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000) who discloses that while dexamethasone induces apoptosis in both CD8+ cells and CD4+ cells, Galectin-9 induces apoptosis in CD8+ cells, but fails to induce apoptosis in CD4+ cells. Thus, a claim drawn to a method of inhibiting apoptosis of any and all cell types lacks enablement. Further, to the extent that apoptosis can be inhibited, many of the disorders recited in claims 64-69 are likely to be exacerbated, rather than ameliorated. Consider the following:

- Kanegane Hirokazu (*Pediatric nephrology* (Berlin, Germany) **18** (5) 454-6, 2003) discloses that mutations in the *Fas* gene result in impaired apoptosis (at least *Fas*-mediated apoptosis), and that as a result of this, autoimmune disease and glomerulonephritis occurs. Thus, one would conclude that inhibiting apoptosis will result in autoimmune disease and glomerulonephritis.

- Strasser A. (*Annals of the New York Academy of Sciences* **917**, 541-8, 2000) discloses that Bim is a member of the Bcl-2 family of proteins, and that Bim induces apoptosis. Strasser further discloses that Bim-deficient mice develop autoimmune disease and glomerulonephritis. Thus, one would conclude that inhibiting apoptosis will result in autoimmune disease and glomerulonephritis.

- Van Den Brande, Jan M. H. (*Annals of the New York Academy of Sciences* **973** 166-80, 2002) discloses that Crohn's disease can be treated by inducing T-lymphocyte apoptosis. The skilled artisan would conclude that if Crohn's disease can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Kacinski B M (*Annals of the New York Academy of Sciences* **941**, 194-9, 2001 discloses that the methods of treating cutaneous T-cell lymphoma that are most successful act by inducing T-cell apoptosis. The skilled artisan would therefor conclude that if cutaneous T-cell lymphoma can be treated by <u>inducing</u> apoptosis, then any attempt to <u>inhibit</u> apoptosis would only exacerbate the patient's condition.

- Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000) discloses that galectin-9 is effective to treat nephritis, and that dexamethasone is also effective in this regard. Both of these agents induced apoptosis of splenic CD8+ cells. The skilled artisan would conclude that if nephritis can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Li X. C. (*Current Opinion in Immunology* **12** (5) 522-7, 2000) discloses that T cell apoptosis is required for transplantation tolerance. The skilled immunologist would conclude that attempts to inhibit apoptosis would result in transplantation rejection.

- Bednarski Jeffrey J. (*Arthritis and rheumatism* **48** (3) 757-66, 2003) discloses that a compound designated Bz-423 induces apoptosis, and is effective to mitigate autoimmune disease such as glomerulonephritis and arthritis. The skilled immunologist would conclude that attempts to inhibit apoptosis would cause autoimmune disease, or at least exacerbate it.

Thus, for a variety of autoimmune, inflammatory and hypersensitivity disorders, inhibiting apoptosis is likely to result in a worsening of the patient's condition. In addition to the foregoing, there is the matter of inhibiting apoptosis in patients who are stricken with cancer, or persons who are pre-cancerous and predisposed to tumor growth. Thus, given that the claimed compounds are more likely to exacerbate a patient's illness than to ameliorate it, the skilled artisan cannot "predict" that therapeutic efficacy can be achieved. [In the response filed 1/24/05, applicants stated that the examiner has characterized claim 38 as allowable, or at least enabled. However, in the Office action mailed 8/18/04, the examiner specifically stated that claim 38 (drawn to a method of inhibiting apoptosis) is not enabled].

In addition to the foregoing, applicants are extrapolating from a showing of caspase inhibition *in vitro* to an assertion that all of the following diseases can be successfully

treated: arthritis, metastasis, infectious diseases, meningitis, salpingitis, septic shock, respiratory diseases, inflammatory condition, cholangitis, colitis, encephalitis, endocerolitis, hepatitis, pancreatitis, reperfusion injury, ischemic diseases, myocardial infarction, stroke, ischemic kidney disease, immune-based diseases, hypersensitivity, auto-immune diseases, multiple sclerosis, bone diseases, neurodegenerative diseases, Alzheimer's Disease, Amylotrophic Lateral Sclerosis (ALS), Huntington's disease, Parkinson's disease, meningitis, spinal chord injuries, liver damage, traumatic brain injury, alopecia, AIDS and toxin-induced liver disease.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Consider, for example, the following:

- Frost, Robert A. (*American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **283** (3) R698-709, 2002) investigated the regulation of TNFα and IL-6 by lipopolysaccharide (LPS) in C2C12 myoblasts and mouse skeletal muscle. Treatment of myocytes with IL-1 or TNF-alpha also increased IL-6 mRNA content, and the increase in IL-6 mRNA due to LPS could not be prevented by pretreatment with antagonists to either IL -1 or TNF. Thus, even if applicants could successfully block all interleukin-1 production using the claimed compounds, interleukin-6 levels could not be controlled, thereby leading to

"unpredictable" results on inflammatory response.

- Meyers, K. P. (*Inflammation* **17** (2) 121-34, 1993) discloses that interleukin-1 receptor antagonist was not active as an antiinflammatory agent in the 24-h pleurisy model (carageenan-induced pleurisy).

- Rosenbaum J. T. (*Archives of Ophthalmology* **110** (4) 547-9, 1992) discloses that interleukin-1 receptor antagonist did not produce significant reduction in inflammation subsequent to an active Arthus reaction or subsequent to the intravitreal injection of 125 ng of endotoxin. Rosenbaum suggests that the failure of IL-1RA to be therapeutically effective may be due in part to the presence of other pro-inflammatory cytokines.

- Brennan (*Clinical and Experimental Immunology* **81**, 278-85, 1990) discloses that TGF-β was effective to inhibit IL-1β production in LPs-stimulated peripheral blood mononuclear cells, but only if the cells were pretreated with TGF-β. The IL-1β production was not inhibited if the TGF-β was applied after the inducing stimulus. The point here is that if a scientist has evidence that a given agent "X" is effective to inhibit production of IL-1β when used prior to stimulation of cells (which stimulation produces the IL-1β), attempting to inhibit production of IL-1β by using agent "X" after stimulation of the cells leads to "unpredictable" results.

- Paris (*Journal of Infectious Diseases* **171**, 161-69, 1995) discloses that IL-1RA was not effective to treat inflammation caused by gram-negative bacteria.

If it were really true that inhibiting the production of interleukin-1 were effective to treat inflammatory conditions, then the skilled artisan would have expected therapeutic success to follow inevitably from such inhibition, or from inhibiting the activation of the receptor for IL-1. However, this is not what one finds. Accordingly, the skilled artisan would expect that in endeavoring to treat inflammatory disorders using compounds that mitigate the production of or efficacy of IL-1, "unpredictable" results will be obtained. Consider also

the following:

- Saez-Torres (*Clinical and Experimental Immunology* **121**, 151, 2000 discloses that peptide T inhibits T cell activation and cytokine production, but that it was not effective *in vivo* to treat EAE (experimental automimmune encephalomyelitis). This supports the assertion that where inflammation and neurodegenerative disorders are concerned, one cannot "predict" therapeutic efficacy on the basis of an *in vitro* assay.

- Hill P. A., (*J Cell. Biochem* **56** (1) 118-30, 1994) discloses that a peptide inhibitor of cysteine proteases is not an effective inhibitor of bone resorption. Thus, one cannot predict the propensity of a compound to inhibit bone resorption based on its propensity to inhibit a thiol protease.

- Steinberg (*The Scientist* **16**, 22, 2002) discloses that when researchers vaccinated transgenic mice that had developed AD-like pathology, placques "melted away". In addition, favorable results were obtained in cognitive experiments with the mice. However, when attempted in humans, the Alzheimer's symptoms worsened. The point here is that where Alzheimer's disease is concerned, extrapolation from experimental result in animals to humans leads to unpredictable results. Steinberg went much further than applicants have, in that he carried out experiments in animals. If extrapolating from rats to humans leads to unpredictable results, it stands to reason that extrapolating from the test tube to diseased humans will also lead to unpredictable results.

- Kitazawa R (*Journal of Clinical Investigation* **94** (6) 2397-406, 1994) investigated factors affecting osteoclastogenesis. Kitazawa discloses that anti-IL-6 Ab inhibited bone resorption *in vitro* but not *in vivo*. Thus, where bone disease is concerned, the skilled artisan would conclude that in attempting to extrapolate form the petri dish to the human, "unpredictable" results are obtained.

- Read S. J. (*Drugs and Aging* **14** (1) 11-39, 1999) discloses (e.g., abstract) that although many drugs are effective in animal models of cerebral ischemia, these drugs have largely failed to fulfil their promise in clinical trials. Applicants have argued that if a compound can inhibit a caspase in vitro, it will be effective to treat ischemia in a human. However, given that extrapolation from animals to humans leads to unpredictable results, it stands to reason that extrapolating from the test tube to diseased humans will also lead to unpredictable results.

Applicants are also asserting that they can successfully treat any and all "infectious diseases". The nature of such diseases is not specified but would include diseases resulting from a bacterial infection, such as one of the following: Anthrax, Bovine Spongiform, Encephalopathy (BSE), Chicken Pox, Cholera, Conjunctivitis, Creutzfeldt-Jakob Disease, Polio, Nosocomial Infections, Otitis Media, Pelvic Inflammatory disease, Plague, Pneumonia, Dengue Fever, Elephantiasis, Encephalitis, Fifth's Disease, Rabies, Rheumatic Fever, Roseola, Rubella, Sexually Transmitted diseases, Helicobacter Pylori, Smallpox, Strep Throat, septicemia, sickle cell anemia, ulcers, Tetanus, Toxic Shock Syndrome, Lassa Fever, Leprosy, Lyme Disease, Typhoid Fever, Measles, Meningitis, Trachoma, Toxoplasmosis, Tuberculosis, Whooping Cough, and Yellow Fever. In addition to the foregoing, viral infections (e.g., hepatitis, HIV, picornavirus) and fungal infections (e.g., candida albicans) would be included. Diseases resulting from parasitic infections would also be included, such as malaria, trypanosomiasis, schistosomiasis, onchocerciasis, leishmaniasis, amebiasis, ascariasis, babesiosis, balantidiasis, enterobius, fiarisis, blood flukes, giaridasis, hookworm, strongyloidiasis, tapeworm, toxoplasmosis, trichinosis, and trichuriasis. As it happens, there is "unpredictability" here too. The following references pertain to fungal infections:

- Buchta, V. (*Mycoses* **44** (11-12) 505-12, 2001) discloses that a patient died from a fungal infection despite being treated with compounds that exhibit anti-fungal activity

in vitro.

- Adam (*Medicine* **65**, 203, 1986) discloses (page 208, col 2) that *in vitro* susceptibility to antifungal agents did not correlate with therapeutic efficacy of the agents.

- Nagasawa M. (*Journal of Infection* **44** (3) 198-201, 2002) discloses that a patient died from a fungal infection despite being treated with compounds that exhibit anti-fungal activity *in vitro*.

- Manfredi R (*Mycopathologia* **148** (2) 73-8, 1999) discloses that two patients died from a cyrotpococcus infection despite being treated with an agent that exhibited anti-fungal activity *in vitro*.

- Wang M. X. (*Cornea* **19** (4) 558-60, 2000) discloses that a patient was treated with an agent that exhibited anti-fungal activity *in vitro*, but that despite this, his fungal sclerokeratitis progressed to endophthalmitis.

- Bhalodia M V (*Journal of the Association for Academic Minority Physicians* **9** (4) 69-71, 1998) discloses that a compound that exhibited anti-fungal activity *in vitro* was not effective to treat a candida infection in a patient.

- Moore M. L. (*Journal of Perinatology* **21** (6) 399-401, 2001) discloses that a premature infant died from a fungal infection despite being treated with a compound that exhibits anti-fungal activity *in vitro*.

- Berman, Judith (*Nat Rev Genet* **3** (12) 918-30, 2002) discloses that many immunocompromised patients die from *Candida* infections in spite of having received various dosages of compounds which exhibit anti-fungal activity *in vitro*.

- van Duin David (*Antimicrobial Agents and Chemotherapy* **46** (11) 3394-400, 2002) has disclosed an example of a compound which exhibits antifungal activity *in vitro* but not *in vivo*.

- Marr K. A. (*Antimicrobial Agents and Chemotherapy* 45 (1) 52-9, 2001) discloses that a patient developed a fungal infection despite prophylactic treatment with a compound which exhibits antifungal activity *in vitro*.

Thus, even if applicants had demonstrated that the claimed compounds can inhibit growth of fungi *in vitro*, it would still follow therefrom that successful treatment of "infections" in animals could not be predicted. "Infections", of course, would include those caused by bacteria. For example, the following would be encompassed:

> Anthrax, cholera, conjunctivitis, nosocomial infections, otitis media, pelvic inflammatory disease, plague, pneumonia, dengue fever, elephantiasis, rabies, rheumatic fever, roseola, rubella, syphillis, gonnorhea, clamydia, helicobacter pylori, "mucosa-associated lymphoid tissue" resulting from helicobacter pylori, smallpox, strep throat, septicemia, sickle cell anemia, ulcers, tetanus, toxic shock syndrome, lassa fever, leprosy, lyme disease, typhoid fever, measles, meningitis, trachoma, toxoplasmosis, tuberculosis, whooping cough, yellow fever, vancomycin-resistant staphylococcus, diarrhea, brucellosis, diptheria, coccidiodiomycosis, and cold sores.

Several of the claims (e.g., 64-70) encompass treatment of HIV/AIDS. With respect thereto, consider the following:

- Mangos (*Texas Medicine*, **86**, 40, 1990) states the following:

  "In spite of ... [therapy against HIV and opportunistic infections], the universal outcome of HIV infection / AIDS is the death of the patients" (see, e.g., abstract).

- As disclosed in Binquet (*AIDS* **12**, 2313, 1998) a total of 556 patients were treated with HIV protease inhibitors for a period of 230 days, and that despite being treated with with HIV protease inhibitors for more than seven months, 24 of the patients had died. Both this reference, and Mangos, teach that death occurs in spite of administration of HIV protease inhibitors. If death is the result of a treatment, one cannot say that success (in the treatment) is predictable.

- Erickson (*Ann Rev Pharm Toxicol* **36**, 545-71, 1996) discloses that resistance of HIV to drugs is a significant problem, and discusses some of the biochemical mechanisms by which such resistance is conferred.

- Matsushita (*Int J Hematol* **72**, 20-27, 2000) discloses that the benefits of anti-HIV therapy, to the extent that they occur at all, are merely transient when only just one or two agents are used.

These references (Mangos, Binquet, Erickson or Matsushita) support the proposition that even if one can demonstrate inhibition of HIV replication *in vitro*, one cannot "predict" therapeutic efficacy in an attempted treatment of an AIDS patient. It is noted that, in the amendment of 1/24/05, applicants have deleted recitation of AIDS from most of the claims (it is still recited in claim 66). However, the "method of treatment" claims still recite the term "immune-based diseases", and as such would include AIDS.

It is not apparent that any of the recited diseases can be successfully treated by the claimed compounds. The reality is that attempting to extrapolate from *in vitro* data to a therapy in humans (or other mammals) leads to "unpredictable" results. For example, Otvos "Insect peptides with improved protease-resistance protect mice against bacterial infection" (*Protein Science* **9** (4) 742-9, 2000) discloses one peptide that is active *in vitro* but not *in vivo* (due to the rapid decomposition in mammalian sera). In the field of ulcer treatment, one may look to the following references, which disclose "failure" in the treatment of such, in spite of *in vitro* efficacy in inhibition of *Helicobacter*:

Phillips, (*Helicobacter* 6, 151, 2001);

Pilotto (*Digestive and Liver Disease* 32 (8) 667-72, 2000);

Leung (*Expert Opin Pharmacother* 1 (3) 507-14, 2000).

As for the issue of antibiotic resistance, the following references discuss this:

Liu (*Advances in Experimental Medicine and Biology* 455, 387 1999)

Monroe (*Current Opinion in Microbiology* 3(5) 496-501, 2000).

Specifically with regard to endotoxin-associated conditions, consider the following: Corriveau C. C. "Antiendotoxin therapies for septic shock" (*Infectious Agents and Disease*, **2** (1) 44-52, 1993) discloses that there have been numerous attempts over the years to treat human septic shock by inhibiting, neutralizing, or clearing endotoxin, and that the results of those attempts support a conclusion of "unpredictability" in the treatment of the same. Thus, extrapolation from *in vitro* data to a therapy in humans (or other mammals) leads to "unpredictable" results.

As for the matter of treating metastasis, this particular pathology is not explicitly recited in the claims. However, tumor growth and metastasis are "immune based" diseases. Accordingly, the "method of treatment" claims encompass the possibility of treating cancer and metastasis. However, if one inhibits apoptosis of tumor cells, the result will be a worsening of the patient's condition, rather than an improvement. One cannot predict therapeutic success under such circumstances.

A matter unrelated to the foregoing concerns the term "protease inhibitor" in claim 40 This claim implies that the compounds can inhibit any protease. However, there is no

evidence that this is the case. Applicants have shown only that the compounds can inhibit caspases. It is rarely the case that a compound can inhibit thiol proteases, metalloproteases, aspartyl proteases, endopeptidases and exopeptidases. There may be a few examples of such, but in most cases this is not what one finds. Issues concerning proteases, active sites of proteases, and inhibition of proteases have been reviewed by Fersht (*Enzyme structure and Mechanism* pp. 18-28, and 302-324, WH Freeman & Co., 1977), Thompson (*Annual Reports in Medicinal Chemistry* **36**, 247-256, 2001) and Storer (*Perspect. Drug Discovery Des.* **6** (Cysteine Proteases), 33-46, 1996). As is evident, there are several classes of proteases, each of which has a different active site. While there may be a few isolated examples of compounds which can inhibit thiol proteases and serine proteases and aspartyl proteases, in general there is no "crossover" between inhibition of different proteases. As for the "working examples", applicants have only shown inhibition of caspases. As for the "unpredictability of the art", the following references are relevant:

- Johnson (USP 6,034,066) discloses (col 7, line 12) a protease that is inhibited by a cysteine protease inhibitor, but not by a serine protease inhibitor.
- Matsuo (USP 4,704,359) discloses (col 3, line 36+) a protease that is inhibited by a serine protease inhibitor, but not by a cysteine protease inhibitor.
- Sato (USP 4,479,937) discloses (col 2, line 30+) a compound which inhibits thiol proteases, but fails to inhibit serine proteases or acid proteases.

Thus, merely because a compound can inhibit a caspase does not mean that the compound

will inhibit all cysteine proteases and all metalloproteases and all carboxypeptidases. The results of such an extrapolation are "unpredictable". In accordance with the foregoing, "undue experimentation" would be required to inhibit proteases other than caspases.

In response to the foregoing, applicants have offered no explanation as to why the examiner's conclusion of "undue experimentation" might be incorrect. Accordingly, no further explanation by the examiner is required at this point.

It is suggested that the term "pharmaceutical" be deleted at every occurrence, that the term "therapeutically effective" be deleted at every occurrence, that the term "treatment" be deleted at every occurrence, and that any claim which recites or implies therapeutic efficacy be cancelled. Also suggested is that claim 40 be cancelled, along with any claims dependent thereon.

✧

- Claim 38 is objected to on grammatical grounds. This claim recites the following:

  "A method of inhibiting apoptosis ... [comprising] contacting a caspase...".

  However, a preposition is missing. Probably what is intended is to recite that the caspase is contacted **with** the compound

- Claim 40 is objected to on grammatical grounds. this claim recites the following:

  "A method protease inhibition...".

It appears that introduction of a preposition would be called for in this situation.

- Claim 55 recites the following: "an unnatural amino acid structures". Here, there is a mismatch between the indefinite article which implies the singular, and "structures", which is in the plural.

- In each of claims 64-69, the term "Amyltrophic" is misspelled.

✧

Claims 37, 38, 40-69 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 37 makes reference to a "structure I", but no structure is identified as being "structure I".

- In claim 37, third line after the structure, the following is recited:

  "which group -N-CH(R^1)CO will produce..."

  However, a hydrogen atom is missing from the amide nitrogen atom.

- Claim 38 recites the following:

  "A method of inhibiting apoptosis ... [comprising] contacting a caspase...".

  There are two issues, the first of which concerns a minor informality. The phrase "a compound of the structure" is preceded by the letter "a". The presence of this letter (in parentheses) implies some sort of list, e.g., that the caspase will be contacted with compounds of other structures in addition to that recited in "a". It is suggested that "(a)" be deleted. [The same issue applies in the case of claim 54].

The second issue concerns the fact that the claim is drawn to a method of inhibiting apoptosis, yet does not require any cells to be present. The claim encompasses the possibility of contacting the compound with a purified caspase in the absence of any cellular material. Under such circumstances, it is difficult to see how apoptosis can be achieved, or inhibition of the same.

- Claim 38 recites that R^5 and $R^{5'}$ "can form a cyclic ring structure in a heterocyclic ring structure". What is intended by this? See also claim 40.

- Claim 38 recites (third line from last) "where X is a, and n is 1-4" What is meant by "X is a"...?

- Claim 40 recites "administration" of the compound, but does not recite a host or recipient. Is it the case, for example, that if the compound is "administered" to a test tube, that a protease present within a human will be inhibited?

- Claim 54 is a method claim, but recites no process steps. What action must the skilled artisan undertake in order to complete the method?

- Claim 54 is dependent on a cancelled claim (claim 39). In addition, claim 39, when pending, was drawn to a compound, not a method (as in claim 54). In addition to the foregoing issues, the claim (claim 54) is grammatically incorrect. Claim 54 recites the following:

  The method... for caspase inhibitor

  It is not clear what is intended. Perhaps what is intended is to recite the following:

  A compound for use as a caspase inhibitor...

- In claim 54, there are five structures presented on page 13 (of 32 total). In the last of these, a furanone ring is linked to the C-terminal aspartyl residue via a

peroxide group (i.e., two oxygen atoms bonded to one another). Is this intended?

- In claim 54, there are five structures presented on page 13 (of 32 total). In the second to last of these, the following group is bonded to the phenyl ring:

$$-CH_2-CH_2-NH-O-CO-O-C_6H_5$$

It appears that the oxygen atom which is bonded to the imino group is unintended. Is this assessment correct?

- In claim 54, there are four structures presented on page 14 (of 32 total). In each of these, an attempt has been made to depict an indole group at the N-terminus. However, in each of these structures, the C-C double bond (within the five-membered ring) is in the wrong position, i.e., it is in the "1,2" position, rather than the "2, 3" position. In addition, in two of the structures, hydrogen atoms are missing from the amide bond.

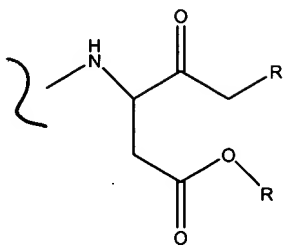
- Claim 55 recites (fourth line from last) "where X is a, and". The term "salt" has been stricken from this passage. Given this, what can "X" be?

- Claim 55 recites (last line) "alkylylaryl or the or base salts". However, this contains a typographical error.

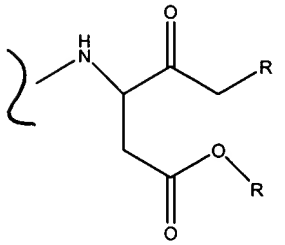
- Claim 55 recites "a compound of the structure". Following this phrase are two structures. It is recommended that each of the two structures be recited in a separate claim. However, if they are going to be present in the same claim, it should be made clear that the two structures are being recited in the alternative. Thus, for example, applicants could recite the following:

A compound of formula I or formula II

The first of the two structures could then be labeled as formula I, and the second as formula II, as indicated below (only partial structures shown, for simplicity):



I



II

- Claim 59 recites the following:

"A caspase inhibitor **as as** a composition comprising".

First, this contains an obvious typographical error. More substantively, the claim is indefinite as to the minimal requirements for one to be in possession of a caspase inhibitor; the claim is also indefinite as to what is permitted for one to be in possession of a caspase inhibitor. In a related vein, it is unclear where the line is drawn between a caspase inhibitor which is just a compound, and a caspase inhibitor which is a composition. For the case of the caspase inhibitor being a composition, what is the second component that must be present? If one has a pure compound, that is a compound and not a composition. On the other hand, if one has a composition, there must be at least one other compound present. What second compound is mandated by the claim? It would be much more clear to claim a composition, rather than an inhibitor. Following are two options:

A composition comprising a caspase inhibitor of the following structure, in

combination with a pharmaceutically acceptable carrier...

A composition comprising a pharmaceutically acceptable carrier and a compound of the following structure in an amount effective to inhibit a caspase...

- In claim 59, there are substituent variables which are defined, but do not appear in the formula, for example, "m" and R^A. The same issue applies in the case of claims 60-61.

- Claims 64-69 are indefinite as to the manifestations of a successful treatment.

- Each of claims 64-69 recite (last two lines) "caspase inhibitor of claim". This phrase should be preceded by the definite article ("the").

- In claim 64, the phrase "the method of treatment" lacks antecedent basis.

- In claim 65, the phrase "the method of treatment" lacks antecedent basis.

- In claim 66, the phrase "the method of treatment" lacks antecedent basis.

- In claim 67, the phrase "the method of treatment" lacks antecedent basis.

- In claim 68, the phrase "the method of treatment" lacks antecedent basis.

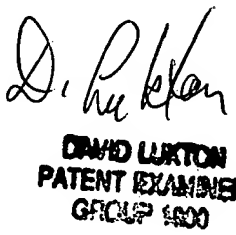
- In claim 69, the phrase "the method of treatment" lacks antecedent basis.

- Claims 64-69 are indefinite as to the host or recipient. For example, if the inhibitor is "administered" to a test tube, will therapeutic benefit accrue to a patient?

- Each of claims 64-69 is indefinite as to what is meant by an "immune-based disease".

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.



No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.